Lipids and cardiovascular disease 3

Triglycerides and cardiovascular disease

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This is the third in a **Series** of three papers about lipids and cardiovascular disease

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After the introduction of statins, clinical emphasis first focussed on LDL cholesterol-lowering, then on the potential for raising HDL cholesterol, with less focus on lowering triglycerides. However, the understanding from genetic studies and negative results from randomised trials that low HDL cholesterol might not cause cardiovascular disease as originally thought has now generated renewed interest in raised concentrations of triglycerides. This renewed interest has also been driven by epidemiological and genetic evidence supporting raised triglycerides, remnant cholesterol, or triglyceride-rich lipoproteins as an additional cause of cardiovascular disease and all-cause mortality. Triglycerides can be measured in the non-fasting or fasting states, with concentrations of 2–10 mmol/L conferring increased risk of cardiovascular disease, and concentrations greater than 10 mmol/L conferring increased risk of acute pancreatitis and possibly cardiovascular disease. Although randomised trials showing cardiovascular benefit of triglyceride reduction are scarce, new triglyceride-lowering drugs are being developed, and large-scale trials have been initiated that will hopefully provide conclusive evidence as to whether lowering triglycerides reduces the risk of cardiovascular disease.

Introduction

More than 25 years ago, mild–moderately high concentrations of triglycerides were regarded as a cardiovascular risk factor, similar to high total and LDL cholesterol.[1–3] Both types of lipid fractions were treated by lipid specialists with the aim of preventing cardiovascular disease, and greatly increased concentrations of triglycerides were treated to prevent acute pancreatitis. These clinical practices were driven by clinicians seeing patients with raised triglycerides and severe cardiovascular disease such as those with remnant hyperlipidaemia, epidemiological evidence, and trials examining the benefit of triglyceride and cholesterol lowering. Equally important was Zilversmit's hypothesis that atherogenesis is a postprandial occurrence, and that raised concentrations of triglycerides and remnant lipoproteins are a main cause of atherosclerosis.[4]

Several scientific breakthroughs, however, lead to more focus on raised LDL cholesterol as the main lipid target for cardiovascular disease prevention. These included first, the identification of LDL receptor mutations as the cause of familial hypercholesterolemia by Brown and Goldstein[5] (who won the Nobel prize in 1985). Second, the LDL-oxidation hypothesis promoted by Steinberg and colleagues that focused attention on LDL.[6] Third, the discovery by Endo in 1976[7] of mevastatin as an inhibitor of HMG-CoA reductase, (the rate-limiting enzyme in cholesterol synthesis) that provided a very effective means of reducing LDL-cholesterol concentrations. This discovery prompted several pharmaceutical companies to develop and test statins, leading to the report of the 4S trial in 1994, which documented reduced cardiovascular disease and reduced all-cause mortality after LDL lowering with simvastatin.[8] This study showed that raised concentrations of LDL cholesterol predisposes an individual to cardiovascular disease, and that LDL lowering is a prime lipid target.

4S and later statin trials also set the standard for evidence-based medicine,[9] ie, treatment of cardiovascular risk factors should result in reduced cardiovascular disease and reduced all-cause mortality. These are valid but very hard criteria to meet. Therefore, as time went by the randomised evidence for treating raised triglycerides to prevent cardiovascular disease seemed weaker and weaker, not least because the expectations changed to include documentation of benefit of triglyceride reduction in patients who were already receiving a statin, evidence that naturally was not generated in the pre-statin era. Raised triglyceride concentrations are strongly associated with low concentrations of HDL cholesterol,[10] and the past 15 years have been dominated by HDL research, with less focus on triglycerides. However, the understanding from genetic studies and randomised trials[11–20] that low HDL cholesterol might not be a cause of cardiovascular disease as originally thought, has generated renewed interest in raised triglycerides.

This Review focuses on the controversies regarding raised triglycerides with respect to their measurement, classification, role in cardiovascular disease, and

Search strategy and selection criteria

We searched the Cochrane Library (between Jan 1, 1988, and May 11, 2014) and the PubMed and Embase databases (between Jan 1, 1950, and May 11, 2014) with the search terms "triglyceride", "triglyceride-rich lipoproteins", or "remnant" in combination with "cardiovascular disease" or "atherosclerosis". We mainly selected publications in the last 5 years, but did not exclude widely referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy, and selected those that we judged were relevant. Review articles and book chapters are cited to provide readers with more details and more references.

treatment. It also emphasises novel developments in epidemiology, diagnostic techniques, genetics, understanding of disease mechanisms, and novel drug developments that aim to treat raised triglycerides for cardiovascular disease prevention. Other reviews detail other aspects of triglycerides and cardiovascular disease, including more comprehensive reference lists.[21–29]

Epidemiology

Unlike individuals with markedly raised cholesterol concentrations as seen in familial hypercholesterolaemia,[5] many individuals with high triglyceride concentrations and so-called chylomicronaemia syndrome do not develop atherosclerosis and cardiovascular disease.[30] This observation initially led to scepticism about the importance of triglycerides in cardiovascular disease; however, this paradox was accounted for by the fact that at greatly elevated concentrations (triglycerides >50 mmol/L), triglyceride lipoproteins are too large to enter into the arterial intima and therefore cannot lead to development of atherosclerosis.[31,32] By contrast, at mild–to–moderately raised triglyceride concentrations (2–10 mmol/L), lipoproteins are small enough to enter into the arterial wall and thus have the potential to accumulate and cause atherosclerosis.[33–35] In this report, we therefore focus on mild–moderately raised triglycerides.

Meta-analyses in the 1990s showed that raised fasting and non-fasting concentrations of triglycerides were associated with increased risk of coronary heart disease, even after adjustment for HDL cholesterol concentrations.[36] Later meta-analyses lent support to these findings,[37] and between 2007 and 2008 three studies based on the Copenhagen City Heart Study and the Women's Health Study suggested that increasingly raised non-fasting triglycerides were strongly associated with increasing risks of myocardial infarction, ischaemic (coronary) heart disease, ischaemic stroke, and all-cause mortality.[38–40] In women, and for concentrations higher than 5 mmol/L versus those less than 1 mmol/L, the age-adjusted risk was increased 17 times for myocardial infarction, 6 times for ischaemic heart disease, 5 times for ischaemic stroke, and 4 times for all-cause mortality during 27–30 years of follow-up. For men, the corresponding risk increases were 5 times, 3 times, 3 times, and 2 times.[38,40] The higher risks for women compared with men in this analysis concurred with previous meta-analyses,[36] and were partly attributable to confounding from higher alcohol intake in men compared with women.[38] Thus, for men with low alcohol intake the risks approached those seen in women.

In 2009, the Emerging Risk Factors Collaboration[41] that included 302 430 individuals from 68 long term, prospective studies, and 12 785 coronary events, similarly recorded that raised fasting and non-fasting triglycerides were associated with an increased risk of coronary (ischaemic) heart disease (adjusted for age and sex,[41] figure 1, top right section). This association was attenuated after adjustment for HDL cholesterol, and abrogated after additional adjustment for non-HDL cholesterol[21,41] (cholesterol in LDL and remnants combined), in accordance with the idea that the cause of ischaemic heart disease is the cholesterol content in remnant particles, rather than raised triglycerides.[10,21,28] Although triglycerides are measured more precisely than HDL cholesterol, triglyceride concentrations vary more on a daily basis than HDL cholesterol, which probably accounts for why HDL cholesterol is statistically more strongly associated with cardiovascular disease than triglycerides.[10,42,43] The Emerging Risk Factors Collaboration[41] also noted that high concentrations of triglycerides were associated with increased age-adjusted and sex-adjusted risk of ischaemic stroke (figure 1, bottom right section). The Emerging Risk Factors Collaboration documented an increased risk of coronary heart disease up to mean raised fasting triglyceride concentrations of around 2·8 mmol/L and increased risk of ischaemic stroke up to around 2·2 mmol/L.

In studies combining the Copenhagen City Heart Study[38,40] and the Copenhagen General Population Study,[42,44] with similar statistical power as for the Emerging Risk Factors Collaboration,[41] increased risks were shown for four different endpoints up to much higher non-fasting triglyceride concentrations than for the Emerging Risk Factors collaboration (figure 1, left and middle sections): in men and women combined for mean, non-fasting triglycerides of 6·6 mmol/L versus 0·8 mmol/L, the age-adjusted and sex-adjusted hazard ratios [HR] were 5·1 (95% CI 3·5–7·2) for myocardial infarction, 3·2 (2·5–4·1) for ischaemic heart disease, 3·2 (2·2–4·7) for ischaemic stroke, and 2·2 (1·8–2·7) for all-cause mortality. Finally, raised triglycerides after LDL lowering with statins were associated with increased cardiovascular risk in some, but not all, randomised trials.[21]

Diagnostic techniques

A lipid profile includes measurement of the total amount of the two most important lipids in the plasma compartment–cholesterol and triglycerides. Similar to any other lipids, these are not soluble in the water phase of plasma, and are therefore carried in lipid particles kept in solution in association with proteins, the so-called lipoproteins. Lipoproteins include HDL—the smallest lipoproteins; LDL—medium-sized lipoproteins; and triglyceride-rich lipoproteins (remnants)—the largest lipoproteins.

For clinical reasons, the cholesterol content in these lipoprotein classes is reported as: HDL cholesterol, LDL cholesterol, and remnant cholesterol. We define remnant cholesterol as the cholesterol content of all triglyceride-rich lipoproteins, ie, chylomicron remnants, VLDL, and intermediate-density lipoproteins (IDL) in the fasting or non-fasting states. In most individuals, chylomicrons are not present in plasma because these particles are degraded to chylomicron remnants very quickly in plasma through

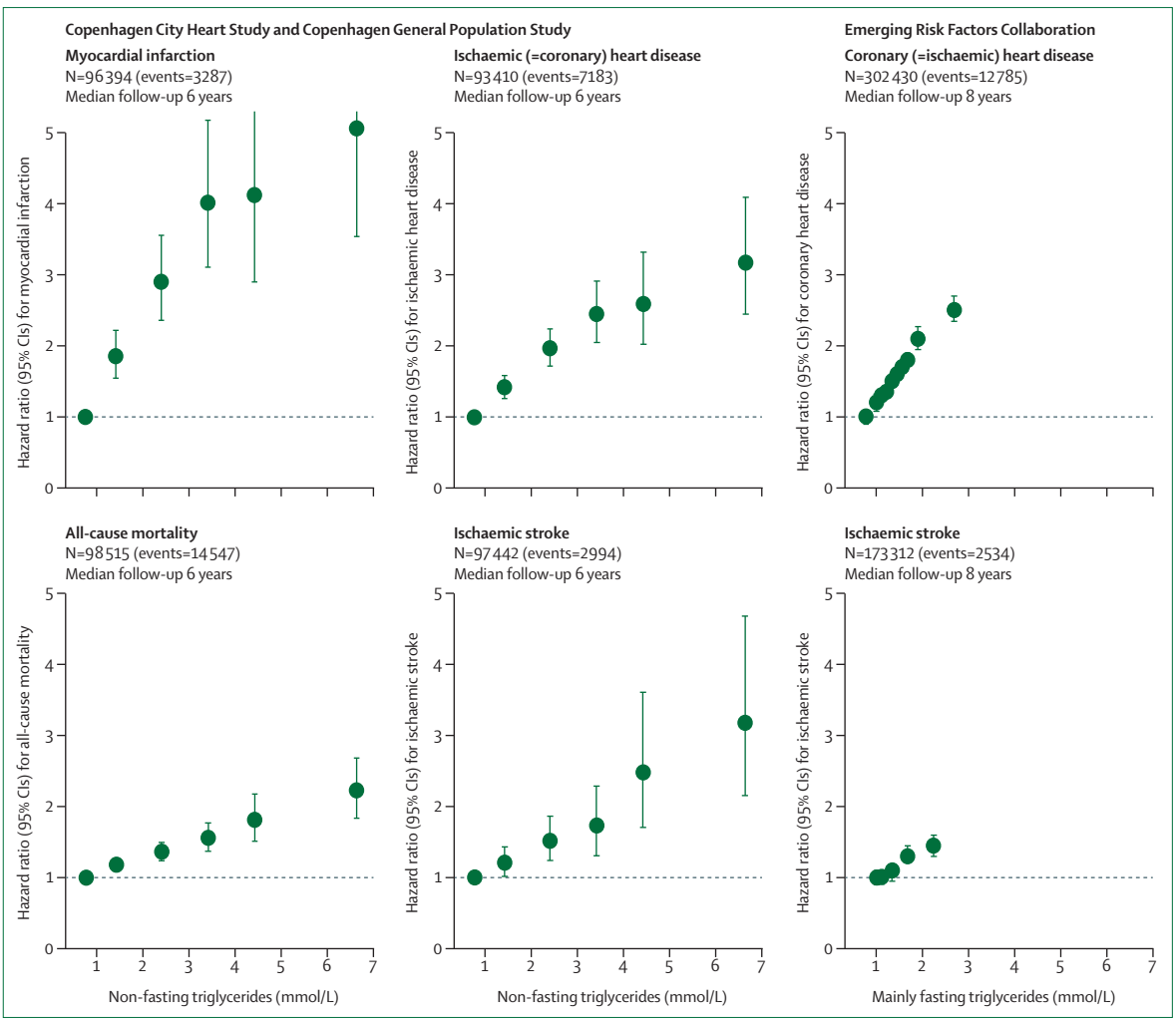

Figure 1: **Observational associations between raised concentrations of triglycerides, and cardiovascular disease and all-cause mortality, in the Copenhagen City Heart Study and Copenhagen General Population Study combined (left and middle sections) and in the Emerging Risk Factors Collaboration (right section)**
Hazard ratios were estimated by Cox proportional hazard regression models, and were adjusted for age, sex, and trial group. Right section adapted from Di Angelantonio and colleagues.[41]

rapid triglyceride hydrolysis by lipoprotein lipase. Some laboratories use the term VLDL cholesterol, which is roughly the same as remnant cholesterol. Remnant cholesterol combined with LDL cholesterol can be assessed as either non-HDL cholesterol or apolipoprotein B, but plasma triglycerides represent a marker for remnant cholesterol only.

Non-fasting versus fasting concentrations

Traditionally, a lipid profile was taken in the fasting state and this is still the case in most countries. However, in some countries—eg, Denmark—a non-fasting lipid profile has been the standard since 2009;[45] if non-fasting triglycerides are more than 4 mmol/L, then a subsequent fasting concentration reading can be requested by the attending physician.

An advantage of non-fasting rather than fasting lipid profile measurements is that the blood-sampling process is simplified for patients, general practitioners, and hospitals, and therefore probably increases compliance to lipid-lowering therapy and monitoring. Triglyceride concentrations on average only increase by 0·2–0·4 mmol/L 2–6 h after eating normal meals;[42,44,46] these increases are clinically unimportant. Furthermore, non-fasting lipid, lipoprotein, and apolipoprotein concentrations, including LDL cholesterol concentrations, predict increased cardiovascular risk.[42] Finally, because most people eat regularly throughout the day and are therefore usually only fasting (defined as at least 8 h since the last meal) for a few hours in the morning, non-fasting lipid concentrations might be a better indicator of average lipid concentrations in the blood rather than fasting concentrations; an oral fat load test is better for establishing postprandial lipid concentrations, but not average lipid concentrations.[24,47] Implementation of non-fasting lipid

profiles in Denmark was very easy, fast, and with no additional costs.

The arguments that are often presented in favour of use of fasting concentrations are: (1) triglyceride concentrations are more stable in the fasting than non-fasting state; however, to the best of our knowledge scientific evidence documenting fasting concentrations as better than non-fasting ones is not available;[21,27,38–41] (2) LDL cholesterol that is calculated according to the original Friedewald equation was developed with fasting individuals; however, directly measured and calculated LDL cholesterol values are highly correlated with each other, both in fasting and non-fasting individuals,[48,49] and modified Friedewald equations are now available for more accurate LDL cholesterol calculations that are based on the variation in both cholesterol and triglyceride concentrations;[50] (3) fasting concentrations have always been used for these measurements and calculations; however, lipid profiles are now the only blood tests that need a fasting status, because even fasting glucose concentrations are being replaced by glycated haemoglobin (HbA_{1c}) concentrations.

Population distribution

27% of individuals in the Copenhagen General Population Study had mild–moderately raised concentrations of triglycerides (2–10 mmol/L), and 0·1% had greatly raised concentrations (>10 mmol/L). For remnant cholesterol measurements, 45% of individuals had concentrations of 0·5–1 mmol/L, and 21% had concentrations of more than 1 mmol/L.

Previous classifications of raised triglyceride concentrations focused on phenotypical differences or different genetic subgroups.[3,27,51] However, novel genetic insights have made these classifications largely obselete, except for the rare disorders remnant hyperlipidaemia (with mild–moderately raised triglyceride concentrations) and chylomicronaemia syndrome (with greatly raised triglycerides).

Remnant cholesterol

Remnant cholesterol is the cholesterol content of triglyceride-rich lipoproteins. Various methods for measuring remnants and remnant cholesterol exist; however, because lipoprotein remnants are different both in composition of lipids and apolipoproteins as a result of different stages of metabolism[5,21] a direct assay that measures all remnants at the same time has not yet been developed. Remnant cholesterol can, however, be calculated as non-fasting total cholesterol minus HDL cholesterol minus LDL cholesterol.[10,38,52,53] An advantage of this calculation is that it can be calculated from a standard non-fasting lipid profile at no additional cost, and although it has not been directly validated by ultracentrifugation methods, raised calculated remnant cholesterol is associated with increased risk of cardiovascular disease.[10,28,52,53]

Genetics and lifestyle

Mild–moderately high concentrations of triglycerides are typically multigenic, and result from the cumulative burden of variants in more than 30 genes together with lifestyle factors, most importantly being overweight or obese.[27] Rare, autosomal, recessive, monogenic disorders can cause greatly raised triglycerides through large-effect mutations in six different genes, ie, *LPL*, *APOC2*, *APOA5*, *LMF1*, *GPIHBP1*, and *GPD1*. However, the most common causes of markedly raised triglycerides also involve high alcohol intake, obesity, or unmanaged diabetes.

The role of triglycerides in cardiovascular disease

Because triglycerides can be degraded by most cells, but cholesterol cannot be degraded by any, the cholesterol content of triglyceride-rich lipoproteins (remnant cholesterol) is more likely to be the cause of atherosclerosis and cardiovascular disease rather than raised triglycerides per se. Indeed, cholesterol not triglycerides accumulates in intimal foam cells and in atherosclerotic plaques, and remnant lipoproteins just like LDL can enter the arterial intima,[4,33,34] but chylomicrons are too large to enter[31,32] (figure 2). Once in the intima, remnants could even be trapped preferentially to LDL, simply because of its larger size and possibly via attachment to extracellular proteoglycans.[22,33,35,54] Lipoprotein-lipase activity at the surface of remnants, either at the vascular endothelium or within the intima, leads to liberation of free fatty acids, monoacylglycerols, and other molecules,[22] each of which

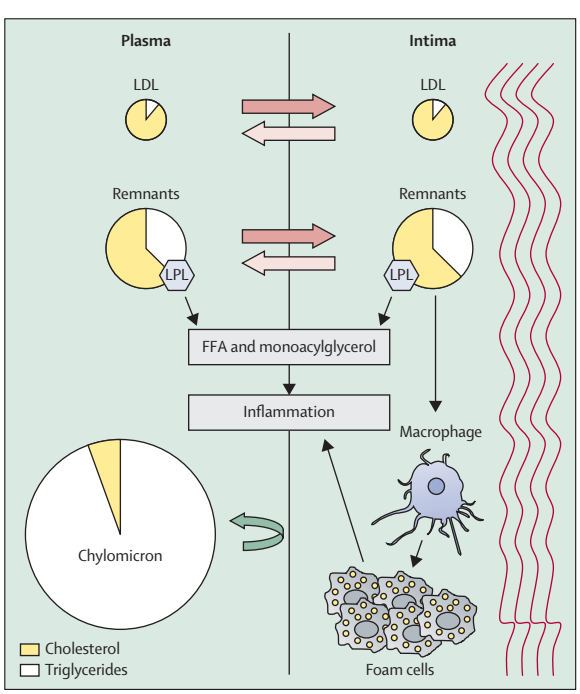

Figure 2: **Suggested role of raised plasma triglycerides and remnant cholesterol in intimal low-grade inflammation and development of atherosclerosis**
Triglycerides and remnant cholesterol could act through triglyceride hydrolysis and cholesterol accumulation in arterial wall foam cells leading to development of atherosclerosis. FFA=free fatty acids, LPL=lipoprotein lipase.

could cause local injury and inflammation.[4,22,55,56] This could possibly account for why lifelong genetically raised remnant cholesterol causes low-grade inflammation.[53] Also, by contrast with LDL, remnants can be taken up directly by macrophages leading to foam cell formation.[22] Although other possible mechanisms have been suggested, perhaps the simplest chain of events is that high triglyceride concentrations are a marker for raised remnants rich in cholesterol, which, upon entrance into the intima, leads to low-grade inflammation, foam cell formation, atherosclerotic plaques, and ultimately cardiovascular disease and increased mortality.

Genetics suggest causality

Experience with inherited disorders encountered in the clinic such as remnant hyperlipidaemia (type 3 hyperlipidaemia) or the so-called familial combined hyperlipidaemia, has for years suggested that raised concentrations of triglycerides and remnant cholesterol predisposes an individual to cardiovascular disease.[3] However, large-scale evidence for this has not previously been available.

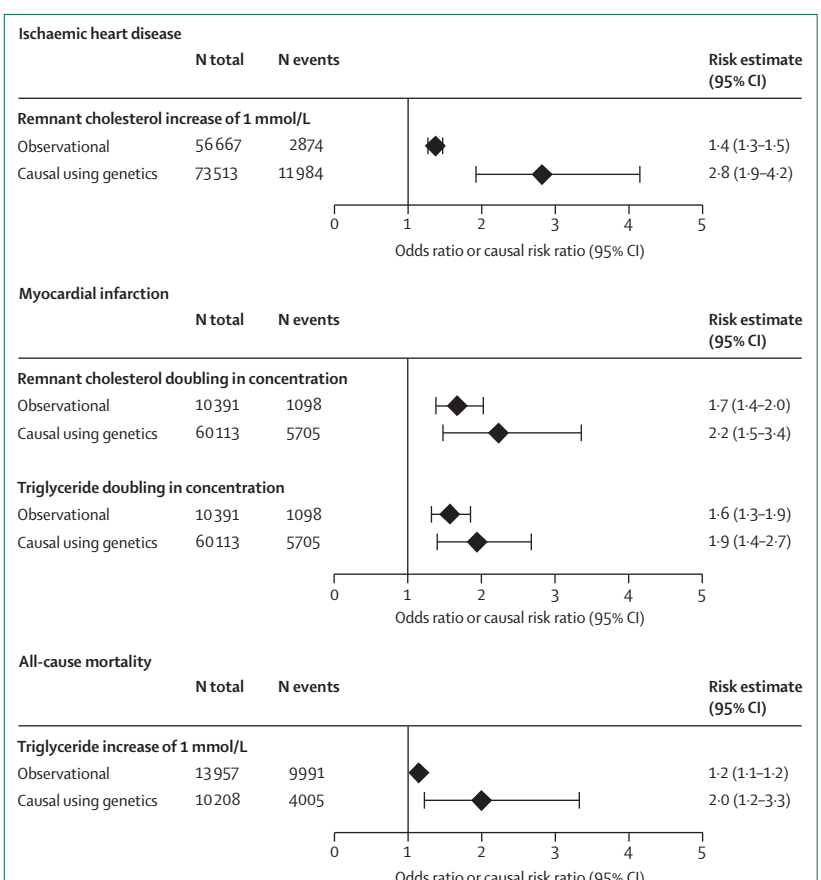

Figure 3: **Observational and causal (by use of genetics) associations of raised remnant cholesterol and triglycerides with risk of ischaemic heart disease, myocardial infarction, and all-cause mortality**
Top section adapted from Varbo and colleagues.[10] Middle section adapted from Jørgensen and colleagues.[52] Bottom section adapted from Thomsen and colleagues.[58] N=number.

Mendelian randomisation studies, just like randomised intervention trials, are typically mainly free of confounding and reverse caution (disease leads to increased risk factors), which are two major difficulties with observational epidemiology,[57] and therefore can provide insight into whether lifelong raised triglycerides and remnant cholesterol are causally associated with low-grade inflammation, cardiovascular disease, and all-cause mortality.[10,52,53,58,59] Essential for successful mendelian randomisation studies is the selection of genetic variants without pleiotropic effects, for which the major difficulty with studying raised concentrations of triglycerides or remnant cholesterol is the inverse association with HDL cholesterol concentrations.[10]

A mendelian randomisation study[10] with genetic variants in several candidate genes that affect the concentrations of remnant cholesterol or HDL cholesterol, or both, showed that an increase of 1 mmol/L in remnant cholesterol was associated with a 2·8-times increased risk of ischaemic heart disease that was not attributable to low HDL cholesterol concentrations; the corresponding observational risk was increased 1·4-times (figure 3, top section). Additionally, a doubling of genetically raised remnant cholesterol concentrations due to *APOA5* genetic variants was associated with a 2·2-times increased risk of myocardial infarction, with a corresponding observational estimate of 1·7-times;[52] for a genetically associated doubling in non-fasting triglycerides, the corresponding risk increases were 1·9-times causally and 1·6-times observationally (figure 3, middle sections). This concurs with findings from another large mendelian randomisation study with a single *APOA5* genetic variant.[59] Furthermore, genetically high concentrations of remnant cholesterol, and thus triglycerides, were associated with increased low-grade inflammation, but this was not the case for genetically high concentrations of LDL cholesterol, which suggests that an inflammatory component of atherosclerosis is driven by triglyceride-rich lipoproteins[53] (figure 2). Finally, with use of genetic variants in *LPL*, a 1 mmol/L increase in triglycerides was associated with a 2·0-times increased risk of all-cause mortality, with a corresponding observational estimate of 1·2-times (figure 3, bottom section); or conversely, that a 1 mmol/L reduction in triglyceride concentrations was associated with a halved risk of all-cause mortality.[58]

Genome-wide association studies (GWAS) have likewise contributed information that suggests a causal association between raised triglycerides and cardiovascular disease.[60,61] An advantage of GWAS-identified genetic variants for raised triglycerides is that many different variants can be identified without a previous hypothesis; however, ruling out pleiotropic effects is more difficult because the functions of many GWAS-identified genetic variants are mainly unknown. Nevertheless, another study supports the suggestion that variants associated with high concentrations of triglycerides were causally associated with cardiovascular disease, even allowing for

low HDL cholesterol.[61] These two studies[10,61] also showed that genetically low HDL cholesterol was unrelated to cardiovascular disease risk, which supports previous similar findings with a mendelian randomisation candidate gene approach.[11–15] However, genetic variation in *CETP* is not only linked to increased HDL cholesterol concentrations, but also to reduced concentrations of triglycerides and LDL cholesterol, and to reduced risk of cardiovascular disease and all-cause mortality.[62]

Taken together, genetic studies strongly support the theory that high concentrations of triglyceride-rich lipoproteins or remnant cholesterol are causal risk factors for cardiovascular disease and all-cause mortality, and that low HDL cholesterol is probably an innocent bystander. Low HDL cholesterol might merely be a long-term marker of raised triglycerides and remnant cholesterol, similar to raised HbA_{1c} concentrations that mark long-term, raised glucose concentrations.[43] Or perhaps, HDL cholesterol might be a marker of cardiovascular health but is non-causal in the process.

Treatment

Detailed advice on lifestyle modifications, including the role of aerobic exercise, dietary fructose, and the Mediterranean diet, and on drug choices to reduce triglycerides, are described elsewhere.[21,27,51,63] For mild–moderately raised triglycerides, the secondary causes of raised triglycerides should be ruled out and treated. Next, lifestyle modification is important, most often weight loss. Then, statin therapy or intensified statin therapy with a potent statin that lowers both triglyceride and LDL concentrations should be implemented; the effect of the statin on triglycerides depends on its capacity to lower LDL cholesterol (eg, the dose) and on baseline triglyceride concentrations. Then, if concentrations of triglycerides are still raised a fibrate can be added. Fish oils and niacin also reduce triglycerides; however, whether they also reduce cardiovascular disease is unknown. Furthermore, glycaemic control has a role in the control of triglyceride concentrations in patients with type 2 diabetes.

Lifestyle modification

For individuals with mild–moderately high concentrations of triglycerides, the most important lifestyle modification is to lose weight through eating less and exercising more.[51] Thus, the aim is to reduce excess calories that otherwise would be deposited as excess fat in the body. Paradoxically, an increased intake of food and supplements that are rich in fish oils reduces triglycerides.[21,23] Reduced alcohol intake is important for people with high triglycerides and high alcohol intake, with the aim of reducing liver and other alcohol-related diseases.

Drug therapies

No large-scale randomised trial has examined the effect of reducing triglycerides on cardiovascular disease risk in people with raised triglycerides. Conversely, most trials (including most statin trials) have excluded participants with triglyceride concentrations that are greater than 4·5 mmol/L. Therefore, results from most reported trials cannot show whether a reduction of triglycerides and remnant cholesterol provides cardiovascular benefit. Despite this, many meta-analyses and reviews have examined the effect of triglyceride-lowering in such trials, which in our opinion has mislead people to believe that the effect of triglyceride-lowering has already been examined and shown to be of no benefit–this is not the case. Indeed, a meta-regression analysis of the effect of triglyceride-lowering in fibrate trials showed that a

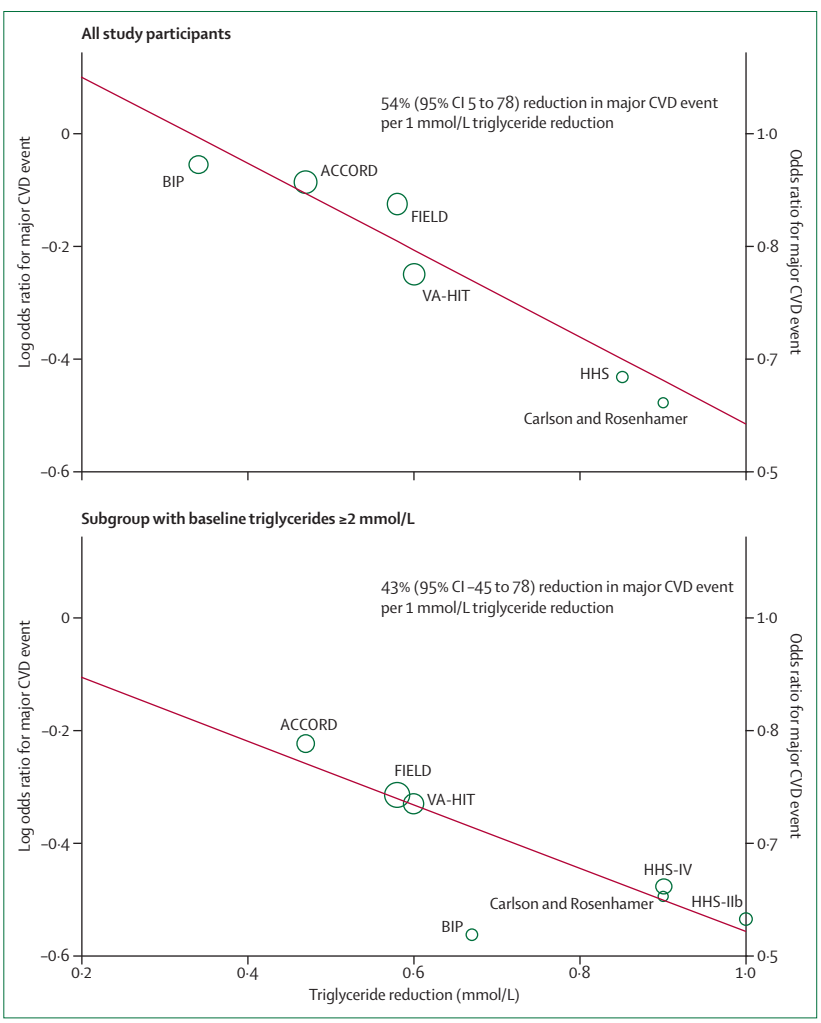

Figure 4: **Association estimated by meta-regression between extent of triglyceride-lowering and reduction in risk of a major cardiovascular event in large controlled trials with fibrates**

Controlled intervention trials with fibrates and post-hoc subgroup analyses for participants with baseline triglycerides ≥2 mmol/Lwere included. For the ACCORD, FIELD, and VA-HIT trials, information on the extent of triglyceride lowering in the subgroup with raised baseline triglyceride concentrations was not available, and therefore the extent of triglyceride lowering for all study participants was used. An overview of the included studies is shown in the supplementary table (appendix). CVD=cardiovascular disease. HHS-IIb=Helsinki Heart Study subgroup of participants with Fredrickson's type IIb hyperlipidemia.[66] HHS-IV=Helsinki Heart Study subgroup of participants with Fredrickson's type IV hyperlipidemia.[66] VA-HIT=The Veterans Affairs High-density lipoprotein Intervention Trial.[67] BIP= Bezafibrate Infarction Prevention study.[68] FIELD= Fenofibrate Intervention and Event Lowering in Diabetes trial.[69] ACCORD= Action to Control Cardiovascular Risk in Diabetes Lipid Trial.[70]

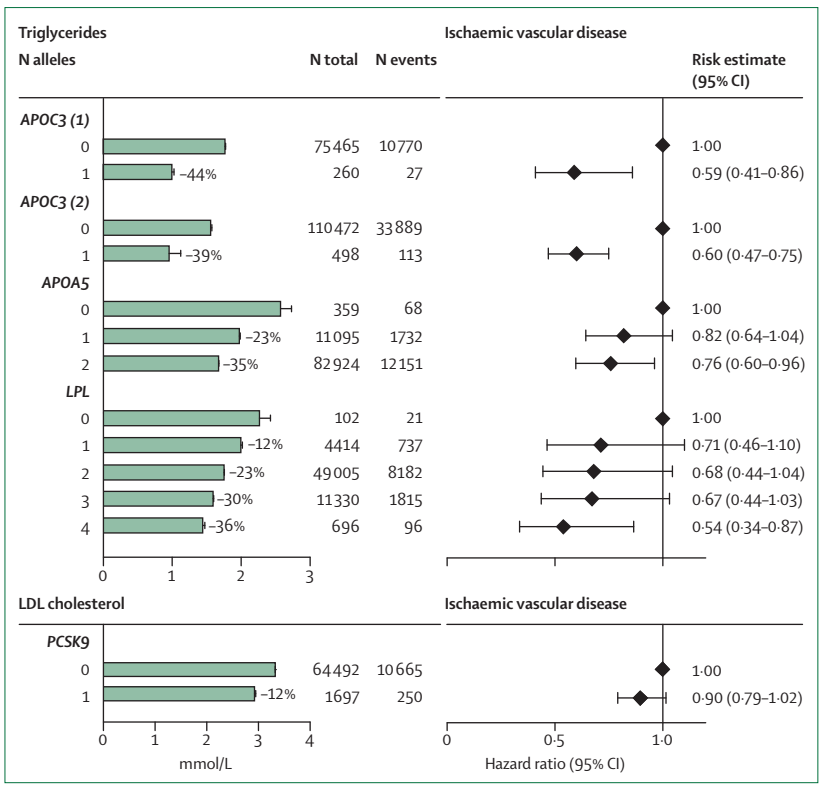

Figure 5: **Association between variants in genes encoding possible triglyceride-lowering drug targets, and extent of triglyceride reduction with corresponding reduced risk of ischaemic vascular disease**
Hazard ratios were estimated by Cox proportional-hazard-regression models for participants from the Copenhagen City Heart Study and Copenhagen General Population Study combined, with adjustments for age, sex, smoking, hypertension, physical activity, and alcohol consumption (except for *APOC3*[2]). N alleles on the vertical axis represent the number of genetic variants carried by the individuals that reduce triglycerides or LDL cholesterol. The *PCSK9* R46L genetic variant is shown for comparison with triglyceride-lowering genetic variants because drugs for PCSK9 inhibition are already used in clinical trials of LDL cholesterol reduction. N=number. Section with *APOC3*(1) adapted from Jørgensen and colleagues.[72] Section with *APOC3*(2) adapted from The TG and HDL Working Group of the Exome Sequencing Project NHLaBI.[73] Section with *APOA5* updated from Varbo and colleagues[10] and Jørgensen and colleagues.[52] Section with *LPL* developed from Wittrup and colleagues[74] and Thomsen and colleagues.[58] Section with *PCSK9* updated from Benn and colleagues.[76]

0·1 mmol/L decrease in triglycerides caused a 5% (95% CI 1–10) reduction in coronary events, with the largest risk reduction in those with baseline triglyceride concentrations of at least 2 mmol/L.[64] Additionally, a controlled trial with 555 consecutive post-myocardial infarction patients given both fibrate and niacin showed that all-cause mortality was reduced by 26%, and ischaemic heart disease mortality was reduced by 36%.[65] In fibrate trials that included post-hoc subgroup analyses for participants with baseline triglycerides of at least 2 mmol/L (appendix, table 1),[43,65–70] a 1 mmol/L reduction in triglycerides reduced coronary events by 54% (5–78) overall and by 43% (–45 to 78%) in those with high triglycerides (figure 4); the risk reduction in those with high triglycerides was statistically significant in the individual studies,[65–69] which included the use of fibrate as an add-on to statin treatment.[70] The magnitude of the effect caused by triglyceride-lowering compares favourably with the reduction of 22% for major vascular events and 10% for all-cause mortality per 1 mmol/L reduction in LDL cholesterol in statin trials;[9] however, the totality of the scientific evidence favouring triglyceride reduction is less than the totality of the evidence favouring LDL reduction.

See Online for appendix

Genetics suggest new drug targets

Evidence from genetic studies suggests potential drug targets for triglyceride reduction, including proteins with the most profound effect on plasma triglycerides such as apolipoprotein C3,[71–73] apolipoprotein A5,[10,52,59] and lipoprotein lipase.[58,74] Lipoprotein lipase is the key triglyceride-degrading enzyme in plasma-, and apolipoproteins C3 and A5 modulate lipoprotein lipase function and affect liver uptake of remnant cholesterol. Figure 5 shows that genetically reduced triglyceride or LDL cholesterol concentrations is associated with reduced risk of ischaemic vascular disease; the size of effect should be compared with that for *PSCK9* R46L heterozygosity in the same Copenhagen individuals[75,76] (figure 5).

For *APOC3* loss-of-function heterozygosity, a reduction in non-fasting triglycerides of 44% was associated with a reduction in ischaemic vascular disease of 41% in individuals from the Copenhagen general population[72] (figure 5). In a parallel study of 18 different cohorts combined, the corresponding reductions were 39% for triglycerides and 40% for coronary heart disease.[73] These findings lend support to findings of reduced coronary artery calcification, a surrogate marker for atherosclerosis, in heterozygotes with *APOA5* loss-of-function mutations.[71]

A reduction in non-fasting triglycerides of 35–36% caused a reduction in ischaemic vascular disease of 24% (4–40) for *APOA5*) and 46% (13–66) for *LPL* compared with non-triglyceride-reducing alleles; (figure 5). These findings agree with previous findings with *APOA5* and *LPL* genetic variants of increased non-fasting triglyceride and remnant cholesterol, and increased risk of ischaemic heart disease.[10,52,53,59,74] Additionally, *ANGPTL3* mutations might cause reduced triglycerides, reduced HDL cholesterol, and reduced LDL cholesterol,[77] making angiopoietin-like 3 another new drug target.

Novel drug therapies

Several new drugs with properties for lowering mild-to-moderately raised or very high concentrations of triglycerides are being developed or are already being tested in clinical trials,[26] including some that are specifically aimed at reducing triglycerides. These drugs include n-3 fatty acids (fish oils), apolipoprotein C3 inhibitors, and *LPL* gene replacement therapy. Other new drugs in development have triglyceride-lowering properties among their functions; these drugs include proprotein convertase subtilisin/kexin type-9 inhibitors, microsomal triglyceride protein inhibitors, apolipoprotein B antisense therapies, cholesteryl ester transfer protein inhibitors, peroxisome proliferator-activated receptor agonists, and diacylglycerol O-acyltransferase-1 inhibitors; at present, the role of such drugs in treating raised triglycerides is unclear.

Although most novel therapies are only in the process of documenting safe triglyceride and remnant cholesterol-reducing properties, two large-scale, randomised, placebo-controlled n-3 fatty acids intervention trials of individuals with raised triglycerides have just been initiated; REDUCE-IT (ClinicalTrials number NCT01492361) and STRENGTH (NCT02104817). REDUCE-IT aims to enrol 8000 patients receiving a statin who either have cardiovascular disease or are at high risk of cardiovascular disease, and also have hypertriglyceridaemia, with an estimated completion date in 2016. STRENGTH aims to enrol 13 000 similar patients who also have low HDL cholesterol; the estimated completion date for this trial is 2019. Compared with previous studies with conventional fish oils, these two trials use purified, concentrated, n-3 fatty acids.

International similarities and differences in treatment recommendations

There are several recent recommendations from Europe[21,27,63,79] and the USA[23,51,80] (appendix, table 2) on how to treat raised triglycerides and other lipid fractions with the aim of preventing cardiovascular disease or acute pancreatitis. Not all of these publications are very clear in their advice. We have therefore tried to simplify the advice described in the various publications on whether the lipid fraction should be treated or not. For mild-to-moderately raised triglycerides, three European publications[21,27,63] and one American[51] publication advise giving treatment to prevent cardiovascular disease, but one European[79] and two American[23,80] publications do not advise such treatment. All publications that discuss very high concentrations of triglycerides agree that this disorder should be treated to prevent acute pancreatitis.[21,23,27,51,63]

Conclusion

The evidence that raised concentrations of remnant cholesterol, marked by raised triglycerides, are an additional causal risk factor for cardiovascular disease and all-cause mortality, is increasing. However, randomised intervention trial evidence is urgently needed, that triglyceride-lowering reduces cardiovascular disease in patients with raised triglycerides. Most desirable would be a placebo-controlled, primary prevention trial of individuals with mild–moderately raised triglycerides without raised LDL cholesterol, with a potent statin in a two-by-two design with addition of another triglyceride-lowering agent. A potent statin is preferred because such drugs have already been shown to reduce cardiovascular disease and all-cause mortality with few side-effects. In individuals already receiving a statin, add-on placebo-controlled, triglyceride-lowering therapy to reduce residual risk is also warranted, and such trials have already started (REDUCE-IT [ClinicalTrials number NCT01492361] and STRENGTH [NCT02104817]).[78] Various controversies regarding triglycerides and cardiovascular disease are summarised in the appendix (panel 1).

Contributors

BGN wrote the first draft of the manuscript, and performed the collection of data and study design. AV drafted the figures. Both authors critically revised the manuscript and figures for important intellectual content, and did the literature search, data analysis, and data interpretation.

Declaration of interests

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